A baby with severe vitamin B_{12} deficiency and heterozygosity in cubilin and MTHFR genes

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Introduction

The vitamin B_{12} (B_{12}) status of babies depends largely on maternal B_{12} status during pregnancy, and on lactation if exclusively breast fed. Physiological changes during pregnancy make laboratory assessment of B_{12} status challenging and B_{12}-deficient states can be masked by iron deficiency. We present a case of a baby with severe B_{12} deficiency whose mother was also deficient.

Case description

A nine month old girl was admitted to the Metabolic Unit at Evelina Children's Hospital for the assessment of developmental delay, abnormal movements (head dropping forward and arms move up; 6-10 episodes per day) and macrocytic anaemia with massive excretion of urinary methylmalonic acid. She was born at term by normal delivery, exclusively breast fed and unable to smile or sit at time of presentation. The introduction of solids at 5 months was unsuccessful because of feeding difficulty and unsafe swallow. She was previously rolling front to back and back to front, but she lost this skill. There is a strong maternal family history of B_{12} and iron deficiency.

On admission baby was pale, coryzal and hypotonic and required intermittent oxygen. She had human metapneumonvirus isolated from her secretions. Her chest x-ray was normal. She was noted to have brief myoclonic jerks - no epileptiform activity was seen on the EEG and the EMG was normal. A brain MRI showed a generalised lack of white matter bulk with evidence of delayed myelination (Figure 1).

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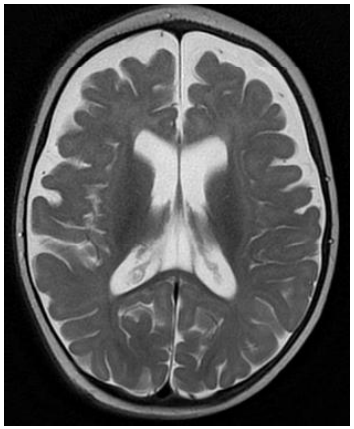

Figure 1 – Axial T2 MRI image: Generalised fullness of CSF spaces with lack of white matter bulk with some evidence of myelination delay. Normal brainstem and generalised thinning of corpus callosum. Normal gyral pattern and no evidence of focal insult

Blood results

Blood investigations revealed macrocytic anaemia, undetectable total B_{12} and holotranscobalamin (holoTC); low methionine, low iron and transferrin saturation (TS); highly elevated urinary and serum methylmalonic acid (MMA) and total plasma homocysteine (Table 1). Folate was normal and coeliac screen negative. Mild IgM deficiency was present but no generalised hypogammaglobulinaemia. There was no proteinuria. MMA and homocysteine normalised after 3 days following IM hydroxocobalamin 1mg/d and iron supplementation and there was improvement in neutrophils and platelet count.

Follow-up two months later: Parents noticed a remarkable improvement in baby's health. She can sit well unsupported and rolls from both back to front and front to back. She is communicating her needs well and is becoming bisyllabic.

	Reference Intervals/ cut-offs	Baseline	Post B_{12} injection (3 days later)	Follow-up (2 months later)
WBC (x10^9/L)	6 - 18	4.2	23.4	16
RBC (x10^{12}/L)	3.60 - 5.20	1.91	2.03	5.22
HB (g/L)	105 - 135	68	72	128
PCV (L/L)	0.360 - 0.440	0.204	0.226	0.376
MCV (fl)	70 - 86	107	111	72
MCH (pg)	23.0 - 31.0	35.7	35.4	24.5
RDW	11.0 - 16.0	24.0	27.5	15.2
PLT (x10^9/L)	150 - 400	91	238	636
Neutrophils (x10^9/L)	2.0 - 6.0	0.4	4.7	4.3
Lymphocytes (x10^9/L)	5.5 - 8.5	3.7	8.9	9.6
Serum folate (nmol/L)	7.0 - 46.4	30.5		
Serum B_{12} (pmol/L)	138 - 652	<62		
HoloTC (pmol/L)	25 - 108	<5	>128	>128
MMA urine (µmol/mmoL creatinine)	0 - 10	840		
MMA plasma (µmol/L)	<0.280	10	0.241	0.097
tHcy (µmol/L)	<15.0	133	11.3	5.1
Methionine (µmol/L)	10 - 53	5		
Ferritin (µg/L)	22 - 275		1233	
Iron (µmol/L)	14.0 - 25.0		9	12
TIBC (µmol/L)	41 - 77		62	51
Transferrin saturation (%)	18 - 71		15	24

Table 1. Selected results from the baby

Genetic results

A panel of genes related to one carbon metabolism and cobalamin disorders was screened by next-generation sequencing but did not provide any explanation for the clinical presentation in this baby. A heterozygous likely pathogenic mutation in the MTHFR gene c.155G>A, p.(Arg52Gln) was identified (paternally inherited) but no second pathogenic variant was detected. A heterozygous cubilin gene variant c.3604G>A, p.(Ala1202Thr) was also detected (maternally inherited) however *in silico* analysis predicted this variant to be benign.

Medication

Hydroxocobalamin 1 mg IM injections daily; Dalivit 0.3 ml bd; Sytron 2.5 mg od;

Levocarnitine and Lansoprazole – stopped at 2 months follow-up visit

	Reference Intervals/ cut-offs	Baseline (At baby's presentation)	Follow up (2 months later)	Follow up (half year later)
WBC (x10^9/L)	4.0 - 11.0	6.1		5.8
RBC (x10^{12}/L)	3.95 - 5.15	5.02		5.08
HB (g/L)	120 - 150	121		139
PCV (L/L)	0.360 - 0.470	0.373		0.413
MCV (fl)	80 - 100	74		81
MCH (pg)	27.0 - 32.0	24.0		27.3
RDW	11.0 - 16.0	15.3		14
PLT (x10^9/L)	150 - 400	210		168
Serum folate (nmol/L)	7.0 - 46.4	23.1	21.7	31.2
Serum B_{12} (pmol/L)	138 - 652	83.5		1734
HoloTC (pmol/L)	25 - 108	<5	>128	335
MMA plasma (µmol/L)	<0.280	1.22	0.086	0.125
tHcy (µmol/L)	<15.0	30.2	6.5	
Ferritin (µg/L)	22 - 275	8		19
Iron (µmol/L)	11.0 - 29.0	6.0	8.0	8.0
TIBC (µmol/L)	41 - 77	66	58	59
Transferrin saturation (%)	18 - 71	9	14	14

Table 2. Selected results of baby's mother

Family history

Investigations showed normal B_{12} status in the father and combined B_{12} and iron deficiency in the mother (Table 2). The mother was negative for intrinsic antibodies and positive for gastric parietal cell antibodies. The mother, 33 yrs, has been anaemic since childhood, intermittently on iron supplementation (Ferrous fumarate) and Pregnacare during first trimester. She has two sons (9 and 4 yrs) who achieved normal milestones. She had three first trimester miscarriages prior to baby's birth. She gives no history suggestive of any neuropathy. She reports being tired although this may be attributed to the care for three children.

B_{12} markers normalised following B_{12} injections, however iron remained low despite oral supplementation.

Conclusion

Maternal B_{12} deficiency, most likely masked by iron deficiency and a normal haemoglobin count on ante natal screening, led to severe B_{12} deficiency in the baby. Exclusive breast feeding and subsequent failure to wean exacerbated the B_{12} deficiency leading to profound functional deficiency of B_{12} causing methylmalonic aciduria and developmental delay. The presence of heterozygous variants in cubilin and MTHFR genes may not be additional contributing factors to B_{12} deficiency in this baby. Resolution of biochemical and haematological abnormalities with marked catch-up of developmental milestones are noted on B_{12} therapy.